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Dimethoxypyrimidines as Novel Herbicides. Part 2. Synthesis and Herbicidal Activity of *O*-Pyrimidinylsalicylates and Analogues*

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Abstract: A new series of the *O*-pyrimidinylsalicylates was synthesized and their herbicidal activity was examined. Some of these compounds showed very strong herbicidal activity under pre- and post-emergent treatment conditions against various kinds of grass and broadleaf weeds. Among these compounds, *O*-(4, 6-dimethoxypyrimidin-2-yl) salicylic acid and its methyl ester were found to exhibit the highest activity. The herbicidal symptoms observed after the treatments included early cessation of plant growth followed by chlorosis, necrosis and plant death. The symptoms were similar to those caused by sulfonylureas and imidazolinones, which inhibit branched-chain amino acid biosynthesis.

Key words: pyrimidinyl salicylates, methyl *O*-(4-chloro-6-methoxypyrimidin-2-yl) salicylate, 2-alkanesulfonylpyrimidines, methyl *O*-(4, 6-dimethoxypyrimidin-2-yl) salicylate, methyl *O*-(4, 6-dimethoxy-*s*-triazin-2-yl) salicylate, acetolactate synthase, sulfonylureas.

1 INTRODUCTION

We have previously found that some 2,4-dimethoxypyrimidines (and triazines) with a phenoxyphenoxy substructure at the 6-position such as compound **1** (Fig. 1) exhibit a marked post-emergent herbicidal activity.[1] Although compound **1** has good activity against various grass and broadleaf weeds, it is phytotoxic against some crops such as rice, wheat and soybean. During the course of the previous study, substitution patterns in the pyrimidine and the terminal phenyl rings of compound **1** were studied. The current work reports the investigation of further changes to the phenoxyphenoxy pyrimidine structure, including various substitutions into the central benzene ring moiety.

In contrast with the ethyl ester **2**, which was herbicidally inactive, its 'regio-isomer' **3** exhibited moderate activity against broadleaf weeds in pre- as well as post-emergent treatments. Symptoms observed on plants of sensitive species after treatment with compound **3** were early cessation of growth followed by necrosis. The activity profiles were similar to those of sulfonylureas, but not to those of the Hill reaction inhibitors.[1] By removing the phenoxy group from compound **3**, the resulting *O*-pyrimidinylsalicylate **6** was found to exhibit highly potent herbicidal activity characteristic of ALS (acetolactate synthase) inhibition. The synthesis and herbicidal activities of the above-mentioned series of compounds are reported here.

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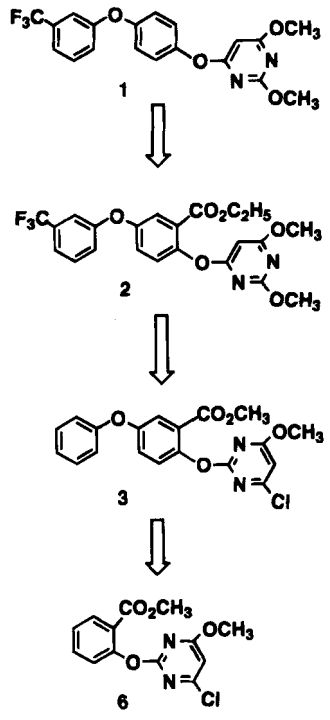


Fig. 1. Discovery of the pyrimidinyl salicylate lead (**6**).

2 MATERIALS AND METHODS

2.1 Instrumental analysis

The methods of instrumental analysis were as described in the previous paper.[1]

2.2 Preparation of compounds

The methoxy pyrimidines **1–5** with the phenoxyphenoxy substructure shown in Table 1 were prepared according to the previous report.[1]

Most of the pyrimidin-2-yl compounds in Tables 2–6 were prepared as outlined in Fig. 2. The 2-substituted pyrimidines were mainly prepared by the reaction of a phenol (*F*) with 2-alkanesulfonyl pyrimidine (*E*).[2] The chloro-methoxy pyrimidines such as compound **6** could also be synthesized by reacting 2,4-dichloro-6-methoxypyrimidine with a variety of phenols (*F*), but this method led to mixtures that were difficult to separate. The 2-substituted pyrimidines obtained via the alkanesulfonyl pyrimidines (*E*) were much easier to purify. Since the overall yield by this method was also higher (yield = 70–90%), it was employed for the synthesis of the *O*-pyrimidinylsalicylate and analogues. The 2-alkanesulfonyl pyrimidines (*E*) were prepared from the corresponding 2-alkylthiopyrimidines (*A*), (*B*), (*C*) and (*D*) by oxidation with oxone or hydrogen peroxide (Fig. 2).

Compound **33** was obtained by oxidation of **32**, which was prepared from the (4-chloropyrimidinyl)salicylates (*I* in Fig. 3). The isomeric 4-phenoxypyrimidines **42** and **43** were prepared by reacting the 4-chloropyrimidines (*G*) with the salicylates (*H*). Compound **41** with the pyridine ring was prepared from 2,6-dichloro-4-methoxypyridine (*G*: $R_1 = Cl$, W = Z = CH). Compounds **49**, **50**, **55** were prepared via compound **48** (Fig. 3). The 5-chloropyrimidine **40** was prepared by chlorination of compound **27** (Fig. 4). The carboxylic acids such as compounds **44**, **52**, **53**, **56**, **58**, **59** were prepared by the hydrolysis of the corresponding esters (Fig. 4). The *N*-methoxyamide **14** was prepared via the imidazolylcarbonyl compound obtained from the carboxylic acid **44** (Fig. 4). Compound **57** with two difluoromethoxy groups on the pyrimidine ring was obtained by reduction of the corresponding benzyl ester (Fig. 4).

The triazines **38** and **39** were prepared by reacting the salicylates (*H*) with the 2-chloro-triazines (*G* in Fig. 3).

The physical properties and the herbicidal activities of these pyrimidine derivatives are shown in Tables 1–6. Most of the pyrimidinylsalicylates and analogues were obtained in good yield (50–90%), except for compounds **2** (18·1%), **13** (40·4%), **26** (29·0%), **42** (37·9%) and **43** (8·8%).

2.2.1 Syntheses of typical compounds

2.2.1.1 2-Methanesulfonyl-4, 6-dimethoxypyrimidine (*E*: $R = CH_3$, $R_1 = R_2 = OCH_3$ *Fig. 2*). To a stirred mixture of 2-methylthio-4,6-dimethoxypyrimidine (*B*: $R = CH_3$, $R_1 = OR_3 = OCH_3$; 186·2 g, 1 mol) and acetic acid (200 ml), sodium tungstate dihydrate (10 g, 0·03 mol) at room temperature was added. To the vigorously stirred solution, hydrogen peroxide (226·6 g, 2 mol) as a 30% aqueous solution was added slowly at 40°C. Stirring was continued at 50°C for an additional 3 h. The excess hydrogen peroxide was destroyed by the addition of an aqueous solution of sodium sulfite, the solid filtered and recrystallized from ethanol to give the title product as colourless crystals, m.p. 116–119°C, yield: 193·5 g (88·6%).

2.2.1.2 4-chloro-6-methoxy-2-benzylsulfonylpyrimidine (*E*: $R = Bzl$, $R_1 = OCH_3$, $R_2 = Cl$ *Fig. 2*). To a solution of 2-benzylthio-4-chloro-6-methoxypyrimidine (*A*: R = Bzl, $R_1 = OCH_3$; 4·3 g, 16 mmol) in methanol (50 ml) oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$; 30 g, 48 mmol) in water (50 ml) was added. After stirring at room temperature for 3 h, the mixture was poured into water. The solid was filtered off and recrystallized from ethanol to give the title product as colourless crystals, m.p. 131–133°C, yield: 4·6 g (95·8%).

2.2.1.3 Methyl O-(4-chloro-6-methoxypyrimidin-2-yl) salicylate (**6**: $X = CO_2CH_3$, $Y = H$, $R_1 = OCH_3$,

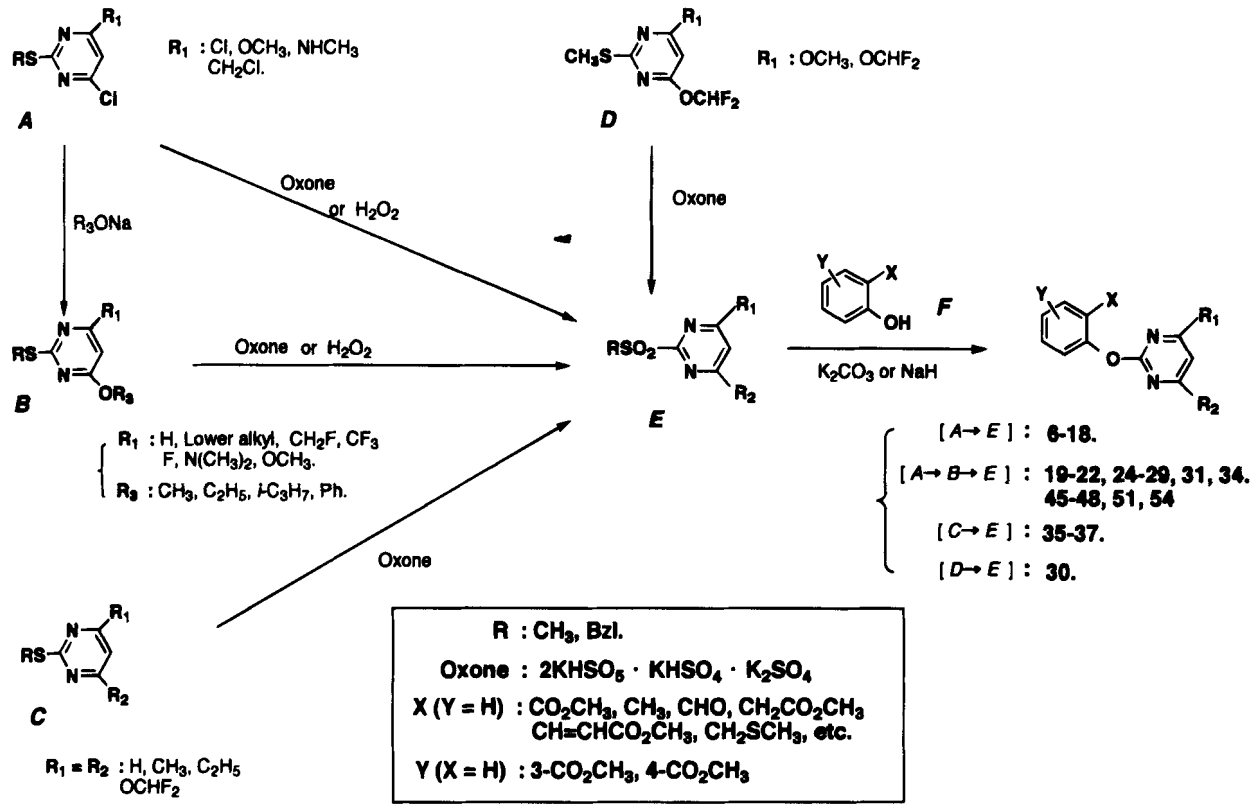


Fig. 2. Synthetic methods for the 2-phenoxypyrimidines.

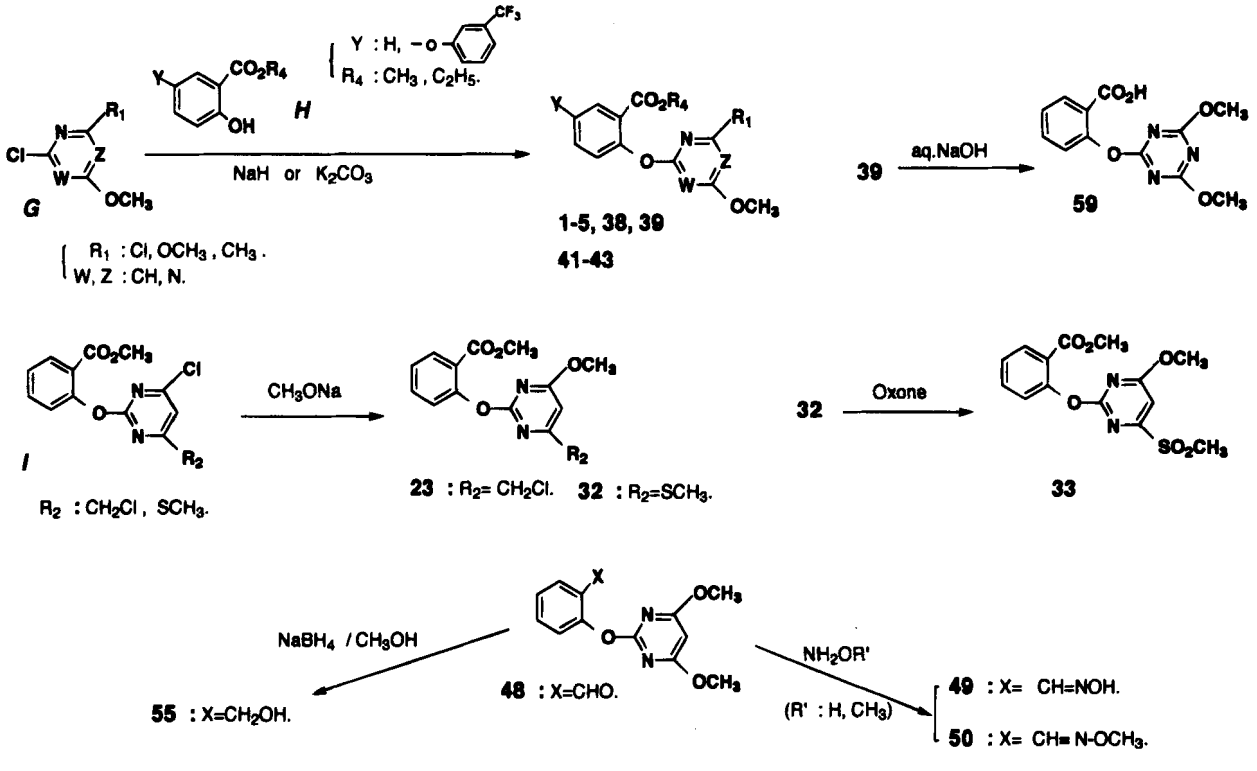


Fig. 3. Synthetic methods for the 2-phenoxypyrimidines and analogues.

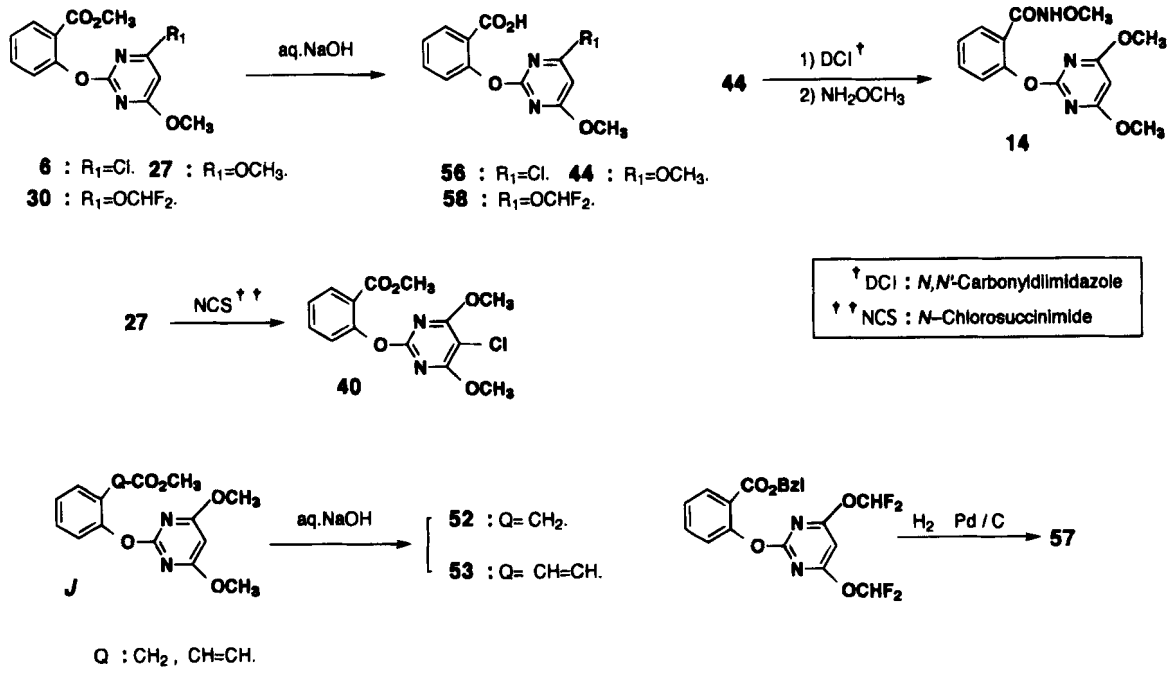


Fig. 4. Synthetic methods for the 2-phenoxypyrimidines.

R_2 = *Cl Fig. 2*). To a mixture of methyl salicylate (*F*: X = CO_2CH_3, Y = H; 2·3 g, 15 mmol) and sodium hydride (25 g, 15 mmol) in benzene (80 ml), a solution of 4-chloro-6-methoxy-2-benzylsulfonylpyrimidine (*E*: R = Bzl, $R_1 = OCH_3$, R_2 = Cl; 4·5 g, 15 mmol) in benzene (20 ml) was added dropwise and stirred for 3 h under reflux. The mixture was poured into water and extracted with chloroform. The extract was washed with water, dried and evaporated under reduced pressure to give a pale yellow oil. This was purified by chromatography on a column of silica gel eluting with ethyl acetate + hexane (1 + 5 by volume) to give compound **6** as colourless crystals, m.p. 54–55°C, yield: 4·1 g (93·2%). [^{1}H]NMR (deuterochloroform) δ ppm: 3·70 (3H, s, CO_2CH_3), 3·80 (3H, s, OCH_3), 6·1 (1H, s, C*H*), 7·0–8·1 (4H, m, Ar—H). IR ν cm^{-1}: 1560 (C=N), 1730 (—CO_2CH_3).

2.2.1.4 Methyl O-(4-methoxy-6-methylpyrimidin-2-yl) salicylate (**20**: *X = CO_2CH_3, Y = H, $R_1 = CH_3$, $R_2 = OCH_3$ Fig. 2*). Following the synthetic method for compound **6**, methyl salicylate (*F*: X = CO_2CH_3, Y = H; 2·8 g, 18 mmol) was treated with anhydrous potassium carbonate (25 g, 24 mmol) in methyl ethyl ketone (80 ml). The mixture was allowed to react with the benzylsulfonylpyrimidine (*E*: R = Bzl, $R_1 = CH_3$, $R_2 = OCH_3$; 5·0 g, 18 mmol) to give compound **20** as a colourless viscous liquid, n_D^{20}: 1·5561, yield: 3·2 g (65·3%). [^{1}H]NMR (deuterochloroform) δ ppm: 2·35 (3H, s, CH_3), 3·70 (3H, s, CO_2CH_3), 3·80 (3H, s, OCH_3), 6·3 (1H, s, C*H*), 7·1–8·1 (4H, m, Ar—H). IR ν cm^{-1}: 1590 (C=N), 1720 (—CO_2CH_3).

2.2.1.5 Methyl O-(4-methoxy-6-methylthiopyrimidin-2-yl)salicylate (**32** *Fig. 3*). To a solution of methyl *O*-(4-chloro-6-methylthiopyrimidin-2-yl)salicylate (*I*: R_2 = SCH_3; 12 g, 40 mmol) in methanol (150 ml) cooled in an ice-bath, 28% sodium methoxide (7·4 g, 40 mmol) was added dropwise. The mixture was stirred at 50–60°C for 6 h, poured into water and extracted with toluene. The extract was washed with water, dried and evaporated. The residual pasty oil was purified by column chromatography eluting with ethyl acetate + hexane (1 + 12 by volume) to give compound **32** as colourless prismatic crystals, m.p. 58–60°C, yield: 6·3 g (53·3%). [^{1}H]NMR (deuterochloroform) δ ppm: 2·35 (3H, s, SCH_3), 3·80 (3H, s, CO_2CH_3), 3·90 (3H, s, OCH_3), 6·3 (1H, s, C*H*), 7·2–8·3 (4H, m, Ar—H). IR ν cm^{-1}: 1730 (—CO_2CH_3).

2.2.1.6 Methyl O-(4,6-dimethoxy-5-chloropyrimidin-2-yl)salicylate (**40** *Fig. 4*). To a mixture of methyl *O*-(4,6-dimethoxypyrimidin-2-yl)salicylate (**27**; 4·0 g, 13·8 mmol) and *N*-chlorosuccinimide (2·0 g, 15 mmol) in carbon tetrachloride (100 ml), a catalytic amount of benzoyl peroxide was added with stirring initially at room temperature and then under reflux for 5 h. The solid was filtered, and the filtrate washed with water, dried and evaporated. The residue was recrystallized from isopropyl ether to give compound **40** as colourless crystals, m.p. 100–102°C, yield: 3·4 g (76·1%). [^{1}H]NMR (deuterochloroform) δ ppm: 3·77 (3H, s, CO_2CH_3), 3·90 (6H, s, OCH_3), 7·1–8·1 (4H, m, Ar—H). IR ν cm^{-1}: 1580 (C=N), 1720 (—CO_2CH_3).

2.2.1.7 Methyl O-(2,6-dimethoxypyrimidin-4-yl)salicylate (**42**: *Y = H, $R_1 = OCH_3$, $R_4 = CH_3$, W = CH, Z = N Fig. 3*). To a mixture of methyl salicylate (4·0 g, 20 mmol) and potassium carbonate (3·8 g, 27 mmol) in *N*,*N*-dimethylformamide (DMF; 200 ml), 4-chloro-2,6-

dimethoxypyrimidine (*G*: $R_1 = OCH_3$, W = CH, Z = N; 4 g, 20 mmol) was added at room temperature with stirring. The mixture was then stirred at 70–89°C for 5 h, poured into water and extracted with benzene. The extract was dried with sodium sulfate and evaporated. The residual oil was purified by column chromatography eluting with ethyl acetate + hexane (1 + 7 by volume) to give compound **42** as a yellow oil, n_D^{20}: 1·5552, yield: 2·0 g (38·5%). [^{1}H]NMR (deuterochloroform) δ ppm: 3·70 (3H, s, OCH_3), 3·80 (3H, s, OCH_3), 3·90 (3H, s, CO_2CH_3), 5·80 (1H, d, C*H*), 7·10–8·05 (4H, m, Ar—H).

2.2.1.8 O-*(4,6-dimethoxypyrimidin-2-yl)salicylic acid* (**44** *Fig. 4*). To a mixture of sodium hydroxide (0·25 g, 6·3 mmol) in water (30 ml) and methanol (30 ml) was added methyl *O*-(4,6-dimethoxypyrimidin-2-yl)salicylate (**27**; 1·7 g, 6 mmol) in small portions. The resulting mixture was stirred at room temperature for 1·5 h, and then distilled under reduced pressure to remove methanol. The residual solution was adjusted to pH 2–3 by the addition of 0·5% aqueous hydrochloric acid, and the precipitated solid filtered, washed with water, dried and recrystallized from diisopropyl ether to give compound **44**, m.p. 150–152°C, yield: 1·4 g (86·5%).

2.2.1.9 N-*Methoxy* O-*(4,6-dimethoxypyrimidine-2-yl) salicylamide* (**14** *Fig. 4*). *N,N'*-carbonyldiimidazole (DCI; 2·3 g, 14·2 mmol) was added in small portions to a mixture of *O*-(4,6-dimethoxypyrimidin-2-yl)salicylic acid (**44**; 2·0 g, 7 mmol) and tetrahydrofuran (80 ml). The resulting mixture was stirred for 2 h under reflux, and cooled to room temperature. Methoxyamine hydrochloride (0·7 g, 8 mmol) and anhydrous pyridine (0·7 g, 8·8 mmol) were added. The resulting mixture was stirred at room temperature for 5 h. The mixture was then diluted with water and extracted with toluene. The extract was washed with water, dried and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with ethyl acetate + hexane (1 + 8 by volume) to give compound **14** as colourless crystals, m.p. 90–92°C, yield: 1·1 g (50·0%). [^{1}H]NMR (deuterochloroform) δ ppm: 3·76 (6H, s, OCH_3), 4·20 (3H, s, $NHOCH_3$), 5·90 (1H, s, C*H*), 6·8–7·7 (4H, m, Ar—H), 10·05 (1H, s, N*H*). IR ν cm^{-1}: 3300 (NH), 1650 (C=N).

2.2.1.10 2-*(2-Hydroxyiminomethylphenoxy)-4,6-dimethoxypyrimidine* (**49** *Fig. 3*). To a suspension of compound **48** (5 g, 19 mmol) in methanol (30 ml), hydroxylamine hydrochloride in water (10 ml) was added dropwise at 10–20°C. The mixture was stirred for 3 h, poured into water and extracted with toluene. The extract was washed with water, dried and evaporated. The residue was recrystallized from isopropyl ether to give compound **49** as colourless prismatic crystals, m.p. 124–127°C, yield: 3·5 g (66·0%). [^{1}H]NMR (deuterochloroform) δ ppm: 3·92 (6H, s, OCH_3), 5·96 (1H, s, C*H*), 7·2–8·1 (4H, m, Ar—H), 8·47 (1H, s, —C*H*=), 8·70 (1H, s, OH). IR ν cm^{-1}: 3500–3000 (=N—OH), 1600 (C=N).

2.2.1.11 2-*(4,6-Dimethoxypyrimidin-2-yl)oxybenzyl alcohol* (**55** *Fig. 3*). A suspension of sodium borohydride (0·65 g, 17 mmol) in methanol (30 ml) was cooled at −10°C in an ice-bath. A solution of compound **48** (3 g, 11 mmol) in methanol (50 ml) was added dropwise at −10–0°C, and the mixture stirred at room temperature for 2 h, poured into water and extracted with toluene. The extract was washed with water, dried and evaporated. The residue was recrystallized from isopropyl ether to give compound **55** as colourless prisms, m.p. 57–59°C, yield: 2·6 g (86·7%). [^{1}H]NMR (deuterochloroform) δ ppm: 2·3–2·7 (1H, s, *OH*), 3·80 (6H, s, OCH_3), 4·5–4·7 (2H, s, CH_2), 6·80 (1H, s, C*H*), 7·0–7·6 (4H, m, Ar—H).

2.2.1.12 O-[*4,6-Bis(difluoromethoxy)pyrimidin-2-yl*]*salicylic acid* (**57** *Fig. 4*). Benzyl salicylate (3·9 g, 17 mmol) was treated with 60% sodium hydride (0·7 g, 17 mmol) in benzene (100 ml). The mixture was allowed to react with 4,6-bis(difluoromethoxy)-2-methanesulfonylpyrimidine[3] (5 g, 17 mmol) to give benzyl *O*-[4,6-bis(difluoromethoxy)pyrimidin-2-yl]salicylate as a colourless viscous liquid, n_D^{20}: 1·5215, yield: 4·7 g (62·7%).

This (3·6 g, 8 mmol) was added to a suspension comprising 10% Pd-C (0·8 g), methanol (30 ml) and acetic acid (10 ml), and the mixture was subjected to catalytic hydrogenation under atmospheric pressure. When the absorption of hydrogen ceased, the catalyst was filtered off and the filtrate was evaporated. The residue thus obtained was dissolved in ethyl acetate, and washed with water, dried and evaporated. The residue was purified by column chromatography eluting with ethyl acetate + hexane (1 + 3 by volume) to give compound **57** as colourless prisms, m.p. 107–109°C, yield: 2·4 g (85·7%). [^{1}H]NMR (deuterochloroform) δ ppm: 6·18 (1H, s, C*H*), 6·0, 7·2, 8·4 (2H, s, CHF_2), 7·3–8·2 (4H, m, Ar—H), 10·8 (1H, s, CO_2H). IR ν cm^{-1}: 3200–2800 (—CO_2H), 1700 (—CO_2—).

2.3 Biological tests

2.3.1 Herbicidal tests

The formulation of compounds and the post-emergence herbicidal tests were carried out as described in the previous report.[1] The growth stages of weeds species, soil type and other test conditions were also identical with those reported previously.[1]

For the pre-emergence test, the suspension of compounds formulated for the post-emergence tests[1] was sprayed onto the soil immediately after the seeds of test plant species were sown. On the 20th day after the spray, the herbicidal activity of each compound was

judged by visual observation of the symptoms of treated plants in comparison with untreated controls. According to the extent of the injury of plants in pre- as well as post-emergence tests, the herbicidal potency was scaled from 0 to 5 according to the following criteria; 5: greater than 90% growth inhibition, 4: 70 to 90% growth inhibition, 3: 40 to 70% growth inhibition, 2: 20 to 40% growth inhibition, 1: 5 to 20% growth inhibition, 0: growth inhibition of less than 5%. The scales follow those defined previously.[1]

For several compounds with prominent herbicidal activity, the activity was retested at 0·25 and 0·5 kg AI. ha^{-1}. Linuron was also applied as the reference herbicide in the wettable formulation at the same rates.

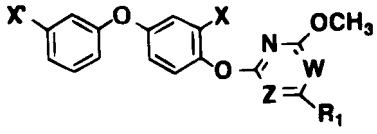
The test results obtained are shown in Tables 1–7.

2.3.2 *Inhibition of the acetolactate synthase preparation*

2.3.2.1 Preparation of the acetolactate synthase sample. Acetolactate synthase was extracted from six-to-seven-day-old etiolated pea shoots which were grown on vermiculite at 27°C.[4] The shoots were homogenized in two volumes of potassium phosphate buffer (0·1M; pH 7·5)

TABLE 1

Post-emergent Herbicidal Activity for the Phenoxyphenoxy Pyrimidines in which the Central Benzene Ring is Substituted



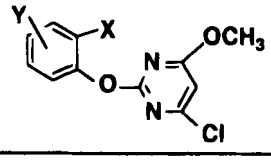
No.	X	X′	R_1	Z	W	m.p. or n_D^{20}	Herbicidal Activity[a,b] Ech	Dig	Pol	Ama	Che	Cyp
1	H	CF_3	OCH_3	CH	N	1·5350	5	5	5	5	5	5
2	$CO_2C_2H_5$	CF_3	OCH_3	CH	N	86–88°C	0	0	0	0	0	0
3	CO_2CH_3	H	Cl	N	CH	93–94°C	1	2	3	3	2	0
4	Cl	CF_3	OCH_3	CH	N	1·5485	3	4	3	5	5	3
5	CH_3	CF_3	OCH_3	CH	N	1·5382	4	4	4	5	5	5

[a] Herbicidal activity was evaluated at a dose of 1 kg AI ha^{-1}.

[b] Ech: *Echinochloa crus-galli*; Dig: *Digitaria adscendens*; Pol: *Polygonum nodosum*; Ama: *Amaranthus retroflexus*; Che: *Chenopodium album*; Cyp: *Cyperus iria*.

TABLE 2

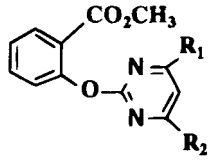
Herbicidal Activity for the Chloro-methoxy-pyrimidinyl Salicylates and Analogues



No.	X	Y	m.p. or n_D^{20}	Herbicidal Activity[a,b] Pre-emergence Ech	Dig	Pol	Ama	Che	Cyp	Post-emergence Ech	Dig	Pol	Ama	Che	Cyp
6	CO_2CH_3	H	54–55°C	5	4	2	4	4	3	3	4	3	5	4	4
7	H	H	73–77°C	0	0	0	0	0	0	0	0	0	0	0	0
8	CH_3	H	1·5675	2	4	0	5	3	0	0	0	0	2	3	0
9	CN	H	136–137°C	0	1	0	1	0	0	0	0	0	0	0	0
10	$CH_2CO_2CH_3$	H	1·5575	0	0	0	1	0	0	0	0	0	0	3	0
11	CHO	H	88–90°C	4	5	5	5	5	5	3	4	3	5	0	3
12	$COCH_3$	H	87–89°C	0	0	0	0	0	0	0	0	0	0	0	0
13	$CONH_2$	H	163–165°C	0	0	0	0	0	0	0	0	0	0	0	0
14	$CONHOCH_3$	H	90–92°C	0	1	0	3	0	1	2	2	0	2	1	0
15	H	3-CO_2CH_3	81–84°C	0	0	0	3	2	0	0	0	0	0	0	0
16	H	4-CO_2CH_3	97–99°C	0	0	0	2	0	0	0	0	0	1	0	0

[a,b] As in Table 1.

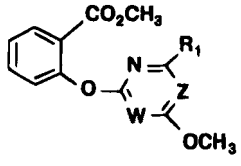
TABLE 3
Herbicidal Activity for the Pyrimidinyl Salicylates



				Herbicidal Activity[a,b]											
				Pre-emergence						*Post-emergence*					
No.	R_1	R_2	*m.p. or* n_D^{20}	Ech	Dig	Pol	Ama	Che	Cyp	Ech	Dig	Pol	Ama	Che	Cyp
6	Cl	OCH_3	54–55°C	5	4	2	4	4	3	3	4	3	5	4	4
17	Cl	Cl	1·5920	0	0	0	0	0	0	0	0	0	0	0	0
18	Cl	$NHCH_3$	120–123°C	0	0	2	3	0	0	0	0	0	3	1	0
19	OCH_3	H	93–96°C	0	0	0	0	0	0	0	0	0	2	0	0
20	OCH_3	CH_3	1·5561	4	5	5	5	4	4	4	3	4	5	5	3
21	OCH_3	C_2H_5	1·5510	0	0	0	1	0	0	0	0	0	0	0	0
22	OCH_3	C_3H_7	1·5467	0	0	0	0	0	0	0	0	1	1	0	1
23	OCH_3	CH_2Cl	1·5678	0	0	0	0	0	0	0	0	0	0	0	0
24	OCH_3	CH_2F	1·5485	4	4	0	5	4	3	2	1	2	3	1	2
25	OCH_3	CF_3	1·5125	0	0	0	0	0	0	0	0	0	0	0	0
26	OCH_3	F	1·5470	4	2	4	4	4	3	1	1	4	1	4	0
27	OCH_3	OCH_3	105–106°C	5	5	5	5	5	5	5	5	4	5	5	5
28	OCH_3	OC_2H_5	1·5465	3	3	3	5	5	5	2	2	2	4	4	1
29	OCH_3	OC_3H_7i	1·5382	0	0	1	3	2	0	0	1	2	2	1	1
30	OCH_3	$OCHF_2$	1·5228	4	4	4	5	5	5	3	2	5	5	5	5
31	OCH_3	OPh	1·5757	0	0	0	0	0	0	0	0	0	0	0	0
32	OCH_3	SCH_3	58–60°C	3	3	4	5	5	4	3	3	4	5	5	4
33	OCH_3	SO_2CH_3	128–133°C	0	0	0	1	0	0	0	0	0	0	0	0
34	OCH_3	$N(CH_3)_2$	79–81°C	0	0	0	2	0	1	2	1	4	4	2	1
35	H	H	92–94°C	0	0	0	0	0	0	1	1	1	1	0	1
36	CH_3	CH_3	1·5603	2	4	3	2	4	4	3	2	2	3	4	1
37	C_2H_5	C_2H_5	1·5491	0	0	0	1	0	0	0	0	2	4	0	0

[a,b] As in Table 1.

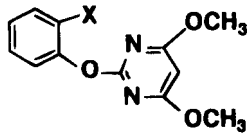
TABLE 4
The Effect of the Nitrogen-Heteroaromatic Ring Structure on the Herbicidal Activity



					Herbicidal activity[a,b]											
					Pre-emergence						*Post-emergence*					
No.	R_1	*Z*	*W*	*m.p. or* n_D^{20}	Ech	Dig	Pol	Ama	Che	Cyp	Ech	Dig	Pol	Ama	Che	Cyp
38	Cl	N	N	78–80°C	0	0	0	1	0	0	0	0	2	3	2	0
39	OCH_3	N	N	64–68°C	5	5	4	5	5	3	4	5	4	5	5	3
40	OCH_3	CCl	N	100–102°C	0	0	0	0	0	0	0	0	0	0	0	0
6	Cl	CH	N	54–55°C	5	4	2	4	4	3	3	4	3	5	4	4
41	Cl	CH	CH	64–65°C	0	0	0	0	0	0	0	0	0	0	0	2
42	OCH_3	N	CH	1·5552	2	2	1	2	2	2	1	0	1	2	1	0
43	CH_3	N	CH	1·5510	0	0	0	0	0	0	0	0	0	0	2	0

[a,b] As in Table 1.

TABLE 5
Herbicidal Activity for the Dimethoxypyrimidinyl Salicylates and Analogues



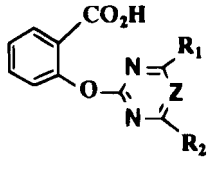
			Herbicidal activity[a,b]											
			Pre-emergence						*Post-emergence*					
No.	*X*	*m.p. or* n_D^{20}	Ech	Dig	Pol	Ama	Che	Cyp	Ech	Dig	Pol	Ama	Che	Cyp
44	CO_2H	150–152°C	5	5	5	5	5	5	5	5	5	5	5	5
45	$CO_2C_2H_5$	1·5411	5	5	5	5	5	5	5	4	4	5	3	4
46	$CO_2C_3H_7$	1·5382	5	5	5	5	5	5	5	4	4	5	4	4
47	$CO_2C_3H_7i$	1·5350	4	4	2	5	5	2	2	2	3	5	5	1
48	CHO	60–63°C	5	5	5	5	5	5	5	5	5	5	5	5
49	CH=N—OH	124–127°C	5	5	5	5	5	5	5	3	3	5	5	5
50	$CH{=}N{-}OCH_3$	1·5681	4	5	5	5	5	5	3	2	1	5	2	2
51	$CH_2CO_2CH_3$	1·5406	1	0	3	1	0	2	0	0	0	3	2	0
52	CH_2CO_2H	124–126°C	4	3	4	4	5	4	3	2	1	4	2	2
53	$CH{=}CHCO_2H$	142–144°C	5	5	5	5	4	5	5	4	5	5	5	5
54	$CH_2SC_2H_5$	1·5652	4	4	5	5	4	4	3	3	4	4	5	4
55	CH_2OH	57–59°C	5	5	5	5	5	5	4	5	3	5	5	5

[a,b] As in Table 1.

containing magnesium chloride (0·5 mmol) and glycerol (100 g litre^{-1}). The homogenate was filtered through one layer of nylon gauze and centrifuged at 15,000*g* for 20 min. Acetolactate synthase was precipitated from the supernatant fluid with ammonium sulfate at 50% saturation. After centrifugation, the pellet was dissolved in an adequate volume (20 ml for 100 g shoots) of the same buffer. Insoluble substances were removed by centrifugation at 15,000*g* for 20 min. The supernatant fluid was then desalted on a Sephadex G-25 column equilibrated with the same buffer and stored at −80°C. Acetolactate synthase activity was not lost during storage for at least one month. This stored enzyme was used for assays immediately after being melted.

2.3.2.2 Assay of the acetolactate synthase activity. The acetolactate synthase assay was carried out in a final volume of 1 ml at 30°C. The final reaction mixture contained potassium phosphate buffer (20 mmol; pH 7·5), sodium pyruvate (20 mmol), thiaminepyrophosphate

TABLE 6
Herbicidal Activity for the Pyrimidinyl Salicylic Acids



					Herbicidal activity[a,b]											
					Pre-emergence						*Post-emergence*					
No.	R_1	R_2	*Z*	*m.p. or* n_D^{20}	Ech	Dig	Pol	Ama	Che	Cyp	Ech	Dig	Pol	Ama	Che	Cyp
43	OCH_3	OCH_3	CH	150–152°C	5	5	5	5	5	5	5	5	5	5	5	5
56	Cl	OCH_3	CH	149–152°C	5	5	3	5	5	4	3	3	3	5	5	4
57	$OCHF_2$	$OCHF_2$	CH	107–109°C	0	0	0	0	0	0	0	0	0	0	0	0
58	OCH_3	$OCHF_2$	CH	120–122°C	2	2	1	4	0	4	1	1	2	3	1	2
59	OCH_3	OCH_3	N	148–152°C	0	2	1	4	1	4	5	5	5	5	5	5

[a,b] As in Table 1.

TABLE 7
Herbicidal Activity of Leading Compounds at 0·5 and 0·25 kg AI ha^{-1}

No.	Application rate (kg AI ha^{-1})	Herbicidal activity[a]											
		Pre-emergence						Post-emergence					
		Ech	Dig	Pol	Ama	Che	Cyp	Ech	Dig	Pol	Ama	Che	Cyp
6	0·5	4	4	1	4	4	2	1	1	1	2	5	0
	0·25	4	4	0	4	4	1	0	0	0	2	2	0
27	0·5	5	5	5	5	5	5	5	5	5	5	5	5
	0·25	4	4	4	4	3	3	5	5	4	5	5	5
39	0·5	4	4	5	5	5	3	4	4	4	5	3	3
	0·25	3	3	5	4	5	2	3	3	3	5	3	2
44	0·5	5	5	2	5	5	5	5	4	5	5	5	4
	0·25	4	5	2	4	5	5	5	4	5	5	5	4
55	0·5	4	3	1	5	5	3	3	2	2	4	4	3
	0·25	2	2	0	5	4	0	2	1	1	3	3	2
Linuron	0·5	1	2	5	5	4	0	2	5	5	5	5	5
	0·25	0	0	5	5	3	0	1	4	5	5	5	4

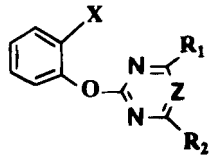
[a] Weed species as in Table 1.

(0·5 mmol), magnesium chloride (0·5 mmol), flavin-adenine dinucleotide (FAD; 0·01 mmol) and various concentrations of each inhibitor. Addition of organic solvents in the reaction mixture was less than 1%. The assays were initiated by adding 0·2 ml of enzyme and terminated by the addition of sulfuric acid (3M; 0·1 mmol). The acetolactate activity was measured as described by Ray[5] with the following modifications. The acidified reaction mixtures were heated for 10 min at 60°C after which 1 ml of 0·5% creatin was added. Then 1 ml of 5% α-naphthol which was freshly prepared in 2·5M sodium hydroxide was added and the solution was heated for an additional 10 min at 60°C. The absorbance of this solution was measured at 525 nm. The I_{50} value for the inhibition was defined as the concentration of each inhibitor which lowered the absorbance 50% of the control in the 30 min fixed time assay. The I_{50} value was estimated from the absorbance–concentration relationship by the probit method.[6,7] The results are shown in Table 8.

3 RESULTS AND DISCUSSION

The substitution pattern in the central phenyl ring of compound **1** was examined using compounds in which one of the ortho-positions (X) to the pyrimidinyloxy

TABLE 8
Effect of the Pyrimidinyl Salicylic Acids and Analogues on Inhibition of Acetolactate Synthase



No.	X	R_1	R_2	Z	Inhibition of ALS $I_{50}(\mu M)$
27	CO_2CH_3	OCH_3	OCH_3	CH	100
44	CO_2H	OCH_3	OCH_3	CH	0·39
48	CHO	OCH_3	OCH_3	CH	59
55	CH_2OH	OCH_3	OCH_3	CH	>100
56	CO_2H	Cl	OCH_3	CH	4·6
57	CO_2H	$OCHF_2$	$OCHF_2$	CH	>100
58	CO_2H	OCH_3	$OCHF_2$	CH	24·8
59	CO_2H	OCH_3	OCH_3	N	5·3
Chlorsulfuron					0·027
Imazapyr					370

group was variously substituted. Table 1 shows the non-X-substituted compound **1** to be most active.

Originally, we had hoped to obtain a compound of higher activity by introducing the carbethoxy group into the *ortho*-position (X) to the pyrimidinyloxy group. Quite a few examples have been found where this type of 'ester-group introduction' is favourable to enhancing the herbicidal activities of various compound classes, for example, the ester grouping substituted at the *ortho* position to the 'electron-withdrawing' oxoimidazolinyl moiety in imazamethabenz.

In this case, the ethyl ester **2** itself was inactive, but its 'isomer' **3** exhibited moderate herbicidal activity. We then prepared compound **6** which lacked the terminal phenoxy group, and found that it exhibited good activity under post-emergent and pre-emergent conditions. Symptoms observed in plants after treatment with compound **6** were early cessation of growth followed by chlorosis, necrosis and death,[8] and suggested that the activity could be of the ALS inhibitor-type.

Using **6** as a new lead compound, various derivatives were synthesized to optimize the herbicidal activity. Initially, we examined whether the methoxycarbonyl substituent at the 2-position on the benzene ring was optimal for herbicidal activity. As shown in Table 2, only the methoxycarbonyl **6** and formyl **11** compounds exhibited good herbicidal activity against grass and broadleaf weeds.

We then investigated the substitution patterns at the 4- and 6-positions on the pyrimidine ring Table 3 whilst the *ortho* methyl ester group was held fixed. The 4,6-dimethoxy compound **27** proved to be considerably more active than the 4-chloro-6-methoxy compound **6**. The combinations of the methoxy with methyl **20**, fluoromethyl **24**, difluoromethoxy **30**, methylthio **32** and the combination of two methyls in compound **36** also exhibited good herbicidal activity. The results suggest that the herbicidal activity is highly dependent upon the small size and the electron-donating property of substituents (R_1, R_2) on the pyrimidine ring.

As shown in Table 4, the introduction of chlorine at the 5-position on the pyrimidine ring, as in compound **40**, diminished the herbicidal activity. Although the triazine analogue **39** exhibited good herbicidal activity, the pyridine analogue **41** was inactive. The effect of the position of the oxygen bridge was examined by compounds **6**, **42** and **43** showing that the bridge is best located at the 2-position on the pyrimidine ring.

As indicated in Table 5, we continued our effort to prepare analogues bioisosteric with the salicylate moiety. The carboxylates **44–47**, the oxime compounds **49** and **50** and the thioether compound **54** had good activity. The formyl compound **48**, α, β-unsaturated carboxylic acid **53** and hydroxymethyl compound **55** were also active, suggesting that compounds that could be transformed into the carboxylic acid in the plant were also active.

Table 6 shows the activity of some of the free acids.

Table 7 shows the herbicidal activity of the most active compounds at lower rates. The dimethoxypyrimidinyl salicylic acid **44** and its methyl ester **27** were the most potent compounds overall. Unfortunately, these compounds were very phytotoxic against crops, thus precluding their practical use.

The mode of action[4] of the *O*-pyrimidinylsalicylates is very similar to that of sulfonylureas, inhibiting the plant enzyme acetolactate synthase (ALS) thereby blocking branched-chain amino acid biosynthesis. As shown in Table 8, both the carboxylate **27** and the carboxaldehyde **48**, which had excellent herbicidal activities, exhibited ALS inhibitory activities considerably weaker than that of the carboxylic acid **44**. This finding supports the idea that the carboxaldehyde **48** is oxidized in the plant to form an active carboxylic acid. The methyl ester **27** can easily be hydrolysed in the plant to form an active carboxylic acid. The inactivity of carboxamide **13** may result from its being difficult to hydrolyse *in vivo*.

The carboxylic acid **44** exhibited an ALS inhibitory activity much higher than that of imazapyr. Pyrimidinylsalicylates are a new class of herbicide differing from both the sulfonylureas and the imidazolinones. The first two classes of compound are structurally unrelated, but both possess a weakly acidic proton and an *N*-heterocyclic ring. These two features are presumably a requisite for herbicidal activity of the ALS inhibitor-type.

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REFERENCES

1. Nezu, Y., Miyazaki, M. Sugiyama, K. & Kajiwara, I., Dimethoxypyrimidines as novel herbicides. Part 1. Synthesis and herbicidal activity of dimethoxyphenoxyphenoxypyrimidines and analogues. *Pestic. Sci.*, in press.
2. Nezu, Y., Nagata, T., Itoh, S. & Masuda, K., Japan Patent JP 63-23870 (1988).
3. Hassig, R., Japan Patent JP 62-281869 (1987).
4. Shimizu, T., Nakayama, I., Nakao, T., Nezu, Y. & Abe, H., Inhibition of plant acetolactate synthase by herbicides, pyrimidinylsalicylic acids. *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **19** (1994) 59–67.
5. Ray, T. B., Site of action of chlorsulfuron. Inhibition of valine and isoleucine biosynthesis in plants. *Plant Physiol.*, **75** (1984) 827–31.
6. Bliss, C. I., The calculation of the dosage–mortality curve. *Ann. Appl. Biol.*, **22** (1935) 15.
7. Finney, D. J., *Probit Analysis*. Cambridge Univ. Press, London, 1952, p. 183.
8. Takahashi, S., Shigematsu, S., Morita, A., Nezu, Y., Clause, J. S. & Williams, C. S., KIH-2031, A new herbicide for cotton. In *Brighton Crop Protect. Conf.—Weeds*, 1991, pp. 57–62.